

How can we reverse bleeding in patients on direct oral anticoagulants?

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Abstract

The direct oral anticoagulants (DOACs), or non-vitamin K antagonist oral anticoagulants (NOACs), including dabigatran, which inhibits thrombin, as well as rivaroxaban, apixaban, edoxaban, and betrixaban, which inhibit coagulation factor Xa, are associated with similar or lower risk of bleeding compared with warfarin. The need for reversal of their anticoagulant effect may occur in patients with life-threatening bleeding or those requiring urgent surgery. Currently, the only specific reversal agent for dabigatran, idarucizumab, is widely available, while andexanet alfa, which reverses factor Xa inhibitors, was approved in the United States in May 2018. Ciraparantag, which has been designed to reverse all DOACs and other anticoagulants, is being investigated in clinical trials. In the absence of licensed reversal agents for the oral factor Xa inhibitors, prothrombin complex concentrates are suggested in patients with life-threatening bleeding. Vitamin K and fresh frozen plasma should not be used to reverse DOACs. This review presents the current evidence regarding bleeding risk on DOACs and the reversal strategies to provide guidance on the management of patients treated with DOACs, who experience serious bleeding.

Key words: bleeding, non-vitamin K antagonist oral anticoagulants, reversal agents

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INTRODUCTION

Non-vitamin K antagonist oral anticoagulants (NOACs) or target-specific oral anticoagulants (TSOACs), which directly inhibit coagulation factor (F) Xa (rivaroxaban, apixaban, edoxaban, and betrixaban) or thrombin (dabigatran), are increasingly used worldwide. The International Society on Thrombosis and Haemostasis has recommended using the term direct oral anticoagulants (DOACs), which will be used in the present review [1]. The DOACs have common characteristics: (i) they are all oral; (ii) they all have rapid absorption and their profile is very similar to that of low-molecular-weight heparin in terms of their pharmacokinetics; (iii) compared to other oral anticoagulants, particularly warfarin, they have remarkably short half-lives (about 12 h); (iv) they have no off-target toxicity. There is no increased risk of leukaemia, liver failure, or other adverse reactions, and any allergic reactions to the DOACs are caused by the dye used in the tablet or capsule, not by the compound itself.

The phase III trials evaluating the efficacy and safety of the DOACs in patients with nonvalvular atrial fibrillation (AF) for the prevention of stroke and systemic embolism [2–6] and the

treatment and prevention of venous thromboembolism (VTE) [7–10] have demonstrated that DOACs have a favourable risk-benefit profile in comparison with a vitamin K antagonist (VKA), warfarin.

However, there are indications in which all physicians will continue to use warfarin for the foreseeable future, most notably in patients with mechanical heart valves and patients with “high-risk” antiphospholipid antibody syndrome [11].

BLEEDING RISK IN PATIENTS ON DOACS

There is compelling evidence that DOACs are as effective in reducing thromboembolic events as warfarin, but they are safer with respect to major and fatal bleeding, in particular intracranial haemorrhage [12, 13]. All large clinical studies of DOACs were conducted without specific antidotes being available.

Clinical registries and large retrospective database studies, including a Food and Drug Administration (FDA) analysis of > 134,000 Medicare patients with AF and Danish nation-wide analyses, demonstrate results consistent with those reported in randomised controlled trials (RCTs) [14–18].

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A systematic review by Chai-Adisaksopha et al. [19], which comprised 12 RCTs (VTE, $n = 7$ and AF, $n = 5$) involving 102,607 patients (Table 1), was the first meta-analysis to examine the impact of bleeding complications of DOACs compared with VKAs in patients with VTE or AF. Patients were treated for 1.6 to 2.0 years in most of the AF trials, while the duration of the VTE trials was between three to 12 months. The average age was from 70 to 73 years in the AF trials and 54 to 57 years in the VTE trials [19]. It has been confirmed that intracerebral bleeding, the most feared haemorrhagic adverse event in patients receiving oral anticoagulants, is reduced by $> 50\%$ while using the DOACs compared with warfarin. Intracranial bleeding represents 8.7% of all major bleeding episodes in VKA users and results in a 46% to 55% mortality rate [20, 21].

Patients with AF or VTE on DOACs have been found to have a lower risk of overall major bleeding (relative risk [RR] 0.72, number needed to treat [NNT] 156), fatal bleeding (RR 0.53, NNT 454), clinically relevant non-major bleeding (RR 0.78, NNT 99), and all bleeding (RR 0.76, NNT 18) [19]. Interestingly, Chai-Adisaksopha et al. [19] did not observe an increased risk of gastrointestinal (GI) bleeding (RR 0.94, 95% confidence interval [CI] 0.88–1.34; Table 1), in contrast to a few published systematic reviews in which DOACs were compared with standard care [12, 22]. An increase in the risk of GI bleeding was observed in the RCTs evaluating dabigatran and rivaroxaban in AF patients [2, 4]. In the RE-LY trial dabigatran 150 mg twice a day (but not dabigatran 110 mg twice a day) increased the risk of major GI bleeding compared with warfarin (RR 1.50, 95% CI 1.19–1.89) [2], whereas in the ROCKET-AF trial rivaroxaban 20 mg once daily increased this risk by 1% (3.2% vs. 2.2%) [4]. The mechanism underlying DOAC-associated GI bleeding is probably the presence of the active drugs in the GI tract, which precipitates bleeding from vulnerable lesions [23]. The discrepancy of the findings of various systematic reviews might be explained by differences in the populations and the comparators used.

There is consensus that the best way to treat bleeding in a patient on an anticoagulant is to avoid having a bleed, and this can be achieved by using the medications with the lowest risk of bleeding.

Warfarin is known to have the highest risk of major bleeding; therefore, a DOAC should be used in many patients at high bleeding risk.

Similarly, a very common cause of avoidable bleeding is coincident use of acetylsalicylic acid (ASA) and a DOAC or warfarin. Concomitant administration of antiplatelet drugs and nonsteroidal anti-inflammatory drugs should be avoided when possible. Most patients who are on warfarin and ASA do not need ASA. In a patient who is receiving any form of oral anticoagulant and any form of antiplatelet agent, the most important thing in the prevention of bleeding is to consider whether they need to be on dual antithrombotic therapy, and

to be confident in discontinuing one of the antithrombotic drugs if it is not indicated. The current European Society of Cardiology guidelines recommend that oral anticoagulation alone, not combination therapy with ASA or another antiplatelet agent, be administered in AF patients with stable coronary artery disease, who did not experience an acute coronary syndrome and/or coronary intervention in the previous 12 months [24, 25].

SPECIFIC STRATEGIES TO REVERSE ANTICOAGULANT EFFECTS OF THE DOACS

In decision-making regarding all clinical problems, good quality evidence is of particular value. Unfortunately, in the field of reversing anticoagulants, including DOACs, there is no level IA evidence, and there will probably never be such evidence.

Idarucizumab

Idarucizumab is a humanised monoclonal antibody fragment, which is a specific reversal agent for dabigatran. It binds with 350-times higher affinity than thrombin to free and thrombin-bound dabigatran within minutes of its administration [26]. This reaction is irreversible [27]. Idarucizumab is primarily eliminated renally [28, 29], and the drug exposure is increased in patients with impaired renal function, which is consistent with higher dabigatran concentrations in such patients. In phase I and II clinical trials, reversal of anticoagulant effects of dabigatran by idarucizumab in a dose-dependent manner has been convincingly demonstrated based on measurements of activated partial thromboplastin time (APTT), thrombin time (TT), diluted TT (dTT), ecarin clotting time, and activated clotting time (ACT) in healthy volunteers and in subjects with reduced creatinine clearance [28, 30, 31].

No effects on coagulation parameters were observed when idarucizumab was administered in subjects not taking dabigatran [28].

Idarucizumab was approved in the United States by the FDA in October 2015 and in Europe one month later. It has become the standard of care for the reversal of dabigatran when it is available [32–34].

The Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) study was a phase III, prospective cohort study designed to show the safety and efficacy of idarucizumab (administered as two consecutive rapid 2.5-g intravenous boluses) in dabigatran-treated patients who present with uncontrolled or life-threatening bleeding (group A) or nonbleeding patients who require emergent surgery or invasive procedure (group B) [35]. The primary outcome of the RE-VERSE AD study was maximum percentage reversal of the anticoagulant effect of dabigatran expressed using dTT and ecarin clotting time performed in a central laboratory. Results of the RE-VERSE AD study were published twice in the *New England Journal of Medicine*, i.e. an interim analysis of the

Table 1. Bleeding risk in randomised controlled trials comparing the efficacy and safety of direct oral anticoagulants (DOACs) versus warfarin in patients with venous thromboembolism or atrial fibrillation

Study (anticoagulant tested)	Publication year	Indication for anticoagulation	Age of patients on DOAC/VKA	Major bleeding HR (95% CI)	Intracranial bleeding HR (95% CI)	Major GI bleeding HR (95% CI)	Fatal bleeding HR (95% CI)
RE-COVER (dabigatran) [75]	2009	Proximal DVT or PE	55.0 ± 15.8/54.4 ± 16.2	0.83 (0.46–1.49)	0.14 (0.01–2.74)	1.79 (0.60–5.32)	0.99 (0.06–15.86)
RE-ly (dabigatran) [2]	2009	AF, ≥ 1 risk factor	71.4 ± 8.6/71.6 ± 8.6	0.88 (0.78–0.98)	0.37 (0.27–0.50)	1.30 (1.07–1.56)	0.65 (0.43–0.99)
RE-MEDY (dabigatran) [76]	2013	Proximal DVT or PE	55.4 ± 15.0/53.9 ± 15.3	0.52 (0.27–1.01)	0.50 (0.09–2.72)	0.62 (0.20–1.90)	0.33 (0.01–8.15)
RE-COVER II (dabigatran) [10]	2014	Proximal DVT or PE	54.7 ± 16.2/55.1 ± 16.3	0.69 (0.36–1.32)	1.01 (0.14–7.14)	0.60 (0.22–1.66)	0.34 (0.01–8.24)
ROCKET AF (rivaroxaban) [4]	2011	Non-valvular AF, CHADS ₂ score ≥ 2	73 (65–78)†/73 (65–78)†	0.87 (0.52–1.45)	0.66 (0.47–0.92)	1.46 (1.19–1.78)	0.49 (0.31–0.78)
EINSTEIN-PE (rivaroxaban) [77]	2012	Acute PE	57.9 ± 7.3/57.5 ± 7.2	0.50 (0.31–0.80)	0.25 (0.07–0.88)	Not reported	0.66 (0.11–3.97)
J-ROCKET AF (rivaroxaban) [78]	2012	Non-valvular AF, ≥ 2 risk factors	71.0 (34–89)†/71.2 (43–90)†	0.87 (0.52–1.45)	0.50 (0.17–1.45)	0.50 (0.19–1.32)	0.33 (0.03–3.20)
EINSTEIN-DVT (rivaroxaban) [79]	2010	Proximal DVT without symptomatic PE	55.8 ± 16.4/56.4 ± 16.3	0.70 (0.35–1.28)	1.00 (0.14–7.06)	0.57 (0.30–1.08)	0.20 (0.02–1.70)
ARISTOTLE (apixaban) [5]	2011	AF, ≥ 1 risk factor	70(63-76)†/ 70(63-76)†	0.70 (0.61–0.81)	0.42 (0.31–0.59)	0.88 (0.65–1.14)	0.62 (0.40–0.94)
AMPLIFY (apixaban) [7]	2013	Proximal DVT or PE	57.2 ± 16/56.7 ± 16	0.31 (0.17–0.55)	0.50 (0.13–2.01)	0.39 (0.16–0.93)	0.50 (0.05–5.54)
ENGAGE-AF-TIMI-48 (edoxaban) [6]	2013	AF, CHADS ₂ score ≥ 2	72 (64–78)†/72 (64–78)†	0.64 (0.57–0.72)	0.39 (0.30–0.50)	0.95 (0.80–1.13)	0.45 (0.31–0.65)
HOKUSAI-VTE (edoxaban) [8]	2013	Proximal DVT or PE	55.7 ± 16.3/55.9 ± 16.2	0.85 (0.60–1.21)	0.28 (0.10–0.75)	Not reported	0.20 (0.04–0.91)

†Median (minimum–maximum)
 AF — atrial fibrillation; CI — confidence interval; DVT — deep vein thrombosis; GI — gastrointestinal; HR — hazard ratio; PE — pulmonary embolism; VKA — vitamin K antagonist

first 90 patients (51 with uncontrolled, life-threatening bleeding [group A] and 39 undergoing urgent surgery or an invasive procedure [group B]) in 2015 [35] and the final analysis of 503 patients (n = 301 [group A] and n = 202 [group B]) in 2017 [36].

Most participants (95.7%) from 39 countries were treated with dabigatran to prevent AF-associated stroke. The median age of participants was 78 years. The efficacy analysis included 461 patients with prolonged dTT or elevated ecarin clotting time, and the median maximum percentage reversal was 100% within 4 h following idarucizumab administration. The median time to cessation of bleeding in bleeding patients was 2.5 h. The median time to initiation of procedure in patients requiring surgery was 1.6 h, and haemostasis was assessed as normal in 93.4% of the participants. The 30-day mortality rate was 13.5% in group A and 12.6% in group B, with most deaths occurring within five days after enrolment.

Of note, nine participants received an additional dose of idarucizumab due to recurrent bleeding or the need for a second urgent procedure, which was related to recurrent prolongation of clotting time due to redistribution of unbound dabigatran from the extravascular to the intravascular compartment.

The RE-VERSE AD study demonstrated the utility of idarucizumab in two groups of patients: those with life-threatening bleeding, in whom very good efficacy in terms of clinical haemostasis was shown, and those referred for urgent surgery, in whom excellent efficacy around the time of surgery was demonstrated [36].

There is a concern that a person reversed from an anticoagulant might suffer from thrombotic complications. In the RE-VERSE AD trial 35 thrombotic events occurred in 31 of almost 500 patients at 90 days. Restart time varied, with a median time of 4.1 days in patients with life-threatening bleeding compared to a much shorter time of 1.4 days in those requiring urgent surgery [36]. Although the half-lives of dabigatran and idarucizumab are prolonged in patients with renal impairment, the adjustment of timing of re-initiation of dabigatran is not necessary. Almost two-thirds of patients had not had their anticoagulants restarted at the time of their thrombotic event. Thus, another key take-home message is that reversed patients must be started back on anticoagulants if they do not have a very high risk of bleeding.

Andexanet alfa

Andexanet alfa is a very specific reversal agent, which binds with high affinity not only to direct FXa inhibitors but also to low-molecular-weight heparins and fondaparinux, indirect FXa inhibitors [37]. Andexanet alfa is a modified human recombinant FXa decoy protein that lacks catalytic activity following replacement of an active-site serine with alanine and with removal of the membrane-binding domain, which precludes this protein from participating in the formation of the prothrombinase complex [37, 38].

In vitro andexanet alfa has been shown to correct increased anti-FXa activity caused by all four DOACs acting as FXa inhibitors, namely: rivaroxaban, apixaban, edoxaban, and betrixaban [38, 39]. Moreover, in animal bleeding models andexanet alfa has been demonstrated to decrease blood loss and restore haemostasis [40–42]. In phase II studies, andexanet demonstrated a rapid, dose-dependent reversal of anticoagulant effects (anti-FXa activity, unbound FXa concentrations, restoration of thrombin potential) in healthy volunteers who received apixaban, rivaroxaban, or enoxaparin [39, 43–45]. Because of its pharmacodynamic half-life of 1 h, andexanet has been evaluated both as a bolus, and as a bolus followed by an infusion, with anti-FXa activity returning to placebo levels within 2 h of completion of dosing.

Results of two randomised, double-blind, placebo-controlled trials (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXa Inhibitors [ANNEXA] trials) performed in healthy volunteers aged 50 to 75 years, who received apixaban (ANNEXA-A) and rivaroxaban (ANNEXA-R) were published [37]. Based on the phase II studies, a higher dose of andexanet was used for rivaroxaban than for apixaban because of higher plasma concentrations and a larger volume of distribution. For ANNEXA-A with apixaban, andexanet was given as a 400-mg intravenous bolus (30 mg/min) in part one and a 400-mg bolus followed by a continuous infusion of 4 mg/min for 120 min (480 mg total) in part two. Corresponding doses in the ANNEXA-R with rivaroxaban were an 800-mg bolus and an 800-mg bolus followed by an infusion of 8 mg/min for 120 min (960 mg total) in parts one and two, respectively. The primary endpoint for the ANNEXA-A and ANNEXA-R studies was the maximum percentage change in anti-FXa activity. Anti-FXa activity was rapidly (within 2–5 min) reduced by 92% to 94% with the andexanet bolus and a reduction of 20% was observed in the placebo group. Following a dose of andexanet there is a fall of anti-Xa activity followed by a slow return of the anticoagulant effect of FXa inhibitor over time. The reversal of anti-FXa activity persists for 120 min with a slow increase as early as after 15 min since the end of administration of this agent. After a bolus of andexanet followed by an infusion, persistent inhibition of FXa is achieved, as long as the infusion is continued.

Of note, andexanet alfa has a good safety profile without thromboembolic or other serious adverse events, including no evidence of the generation of neutralising antibodies against this agent or FX or FXa. Transient increases in markers of blood coagulation activation reported during the ANNEXA-A and ANNEXA-R trials (namely D-dimer and prothrombin fragments 1.2) in study participants have uncertain clinical relevance.

The ANNEXA-4 phase IIIb to IV study assessed the efficacy and safety of andexanet alfa in patients treated with FXa inhibitors with acute major bleeding, but not in those anticoagulated subjects who require emergency or urgent procedures, which is in contrast to the REVERSE-AD trial

[36, 46]. The final results of this study should be reported in the near future.

At the present time, FXa inhibitors do not have reversal strategies in Europe or in Canada. On May 4th, 2018 andexanet alfa was approved in the United States. However, there are some caveats regarding this reversal agent: (1) it will be available in very limited quantities for at least a year, and then it will be more widely available only in the United States; (2) the company estimates that it will cost about USD 25,000 for the lower dose and USD 50,000 for the higher dose, which effectively means that the vast majority of patients treated with rivaroxaban or apixaban will never have access to it, particularly outside the United States.

Ciraparantag

Ciraparantag is a small, water soluble, cationic synthetic molecule designed to specifically bind to unfractionated heparin, low-molecular-weight heparin, and DOACs, both thrombin and FXa inhibitors. This agent may be a universal antidote; however, it is in an early stage of development. The mechanism of its inhibitory effects involves noncovalent hydrogen bonding and charge-charge interactions. Ciraparantag has been demonstrated to normalise clotting time within 10 to 30 min of administration [47]. Ciraparantag has been investigated as an antidote for edoxaban (60 mg) in a double-blind, placebo-controlled study [48]. A single intravenous dose of ciraparantag (100 to 300 mg) reversed anticoagulant effects within 10 min and sustained for 24 h in 80 healthy subjects. When administered to healthy subjects, ciraparantag is safe and well tolerated with minor, non-dose-limiting adverse events such as periorbital and facial flushing and cool sensation [48].

NON-SPECIFIC REVERSAL STRATEGIES

The available factor Xa inhibitor reversal strategies rely on non-specific strategies of unknown effectiveness. Prothrombin complex concentrates (PCCs) are widely used in those strategies but with no evidence of efficacy.

A prospective multicentre observational study, or a large case series, published in July 2017, described how physicians actually deal with bleeding on DOACs in the real world [49]. It demonstrated that reversal strategies are inconsistent with large variability in practice. Bleeds occurred in patients at an average age of almost 82 years. Looking at 460 bleeds that occurred in patients on DOACs, the authors reported that almost 20% of those patients received vitamin K, which is useless in such clinical situations. It has no possibility of having any effect but was given probably because many of these patients had a prolonged international normalised ratio (INR) due to rivaroxaban.

Tranexamic acid, an antifibrinolytic agent effective in trauma or postpartum haemorrhages, acts as a lysine analogue that impairs plasminogen activation on fibrin. In patients on DOACs its efficacy is uncertain; however, it might be used.

Fresh frozen plasma is ineffective in patients bleeding on DOACs but was used in about 10% of patients reported by Xu et al. [49]. Fresh frozen plasma may be used as a plasma volume expander in patients following transfusions, but its shortcomings are numerous and involve factors limiting its effectiveness, and it has a higher risk of transfusion reactions and acute heart failure, especially in the elderly, due to an increased volume and oncotic load [50–53].

Protrombin complex concentrates are plasma-derived products that contain three (factors II, IX, and X) or four (addition of factor VII) clotting factors in addition to variable amounts of heparin and the natural coagulation inhibitors, protein C and protein S, which are used, among others, to reverse anticoagulant effects of VKA in severely bleeding patients. Activated PCC (aPCC), known as factor VIII inhibitor bypassing activity, contains activated factor VII along with mainly nonactivated factors II, IX, and X. Animal studies have demonstrated that PCCs have variable ability to normalise anticoagulation parameters and to prevent or attenuate bleeding across the DOACs [53–60]. Three randomised, placebo-controlled studies have been performed in 12 to 93 healthy volunteers who received DOACs. They demonstrated that PCCs can reverse the anticoagulant effect of rivaroxaban and edoxaban with complete reversal with 50 U/kg and partial reversal with 25 U/kg, while no similar effect (no changes in TT, APTT, endogenous thrombin generation lag phase, and ecarin clotting time) was observed in subjects on dabigatran [61–64]. In vitro studies in healthy volunteers demonstrated that aPCCs added to plasma containing DOACs have a more potent effect on coagulation parameters than PCCs alone [65, 66]. If PCC or aPCC is selected to treat a patient with major or life-threatening DOAC-associated bleed, acknowledging the lack of evidence for this intervention, a dose of 50 U/kg of PCC or aPCC is recommended.

Another therapeutic option in bleeding patients on DOACs is recombinant activated factor VII (rFVIIa, Novo-seven). A few in vitro and ex vivo studies demonstrating variable efficacy of rFVIIa to reverse coagulation parameters attributable to DOACs [65, 66–73] have been published. There have been a few case reports of patients receiving this agent due to life-threatening bleeding, although there have been no clinical trials investigating this strategy. Based on limited experience, a dose of 90 U/kg used in patients with acquired haemophilia A has been proposed to limit the most severe bleeding on DOACs [49].

Interestingly, reasonable non-specific strategies that might be used in emergency situations including PCC, aPCC, or rFVIIa were all used in fewer than 20% of patients with serious bleeding on DOACs in the real-life study by Xu et al. [49].

Experts suggest that hospitals should adopt anticoagulation reversal protocols developed by a multidisciplinary team involving intensivists, cardiologists, haematologists, surgeons, gastroenterologists, neurologists, and others. Examples of

such protocols are available for clinicians, but they should be adapted to local circumstances [74]. By standardising approaches to care and minimising the risk of missing key interventions, such studies are likely to improve care for patients with bleeding.

EXAMPLES OF DECISION-MAKING REGARDING BLEEDING PATIENTS ON DOACS

Case 1

A 79-year-old man with permanent AF receiving dabigatran 150 mg twice a day reported to the emergency department presenting with new hemiparesis and aphasia. Computed tomography revealed subdural haemorrhage. His blood tests were as follows: INR of 1.1, APTT of 35 s, and TT of 135 s (reference range below 30 s). The question is whether he should receive some form of reversal agent.

The decision was not to administer idarucizumab. The thrombin time of 135 s indicates that he still has some dabigatran in circulating blood, but the thrombin time goes up very quickly with dabigatran, so the level of 135 means he probably does not have very much of the drug in the system. And by the time he actually got the reversal agent administered he would probably have no dabigatran left.

Case 2

A 71-year-old man presented to the emergency department at 8:00 p.m. on a Saturday night with abdominal pain and hypotension. Imaging revealed a ruptured abdominal aortic aneurysm. He had non-valvular AF, arterial hypertension, dyslipidaemia, and a history of ischaemic stroke one year ago. He was taking apixaban 5 mg twice a day. His last dose of apixaban had been taken approximately 12 h previously. The surgeon called the lab and asked for proof that there was no anticoagulant effect present. The laboratory examination was as follows: haemoglobin 10.2 g/dL, platelet count 292,000/ μ L. The prothrombin time, INR, and APTT were normal. The anti-Xa level was sent, but will not be available in a realistic time-frame. The question is whether this person has a discernible anticoagulant effect and if we should do something to intervene to reduce the risk of bleeding when he goes for surgery. An immediate decision is needed; vascular surgeon recommends emergent open repair; 2 h is too long to wait. What strategy should be recommended?

One might think that the normal results of the coagulation tests indicate that the person does not have an anticoagulant effect; however, apixaban does not produce any effect on the most commonly available coagulation tests. Therefore, if a person is taking apixaban, the INR, prothrombin time, APTT, and thrombin time are all useless. If this person receiving apixaban has a ruptured abdominal aortic aneurysm, the surgery should be performed and the surgeon should be advised that the patient may have increased risk of bleeding. Prothrombin complex concentrates are widely used to

treat bleeding in patients taking DOACs, and they might be considered if the person bleeds excessively in the operating room. In all likelihood the patient is not going to have abnormal bleeding because the apixaban was taken 12 h earlier.

SUMMARY

Reversal strategies in patients receiving DOACs depend on the anticoagulant involved, the location and severity of the bleeding, and/or the urgency of the invasive procedure. The available specific reversal agent for dabigatran, idarucizumab, is used infrequently for the reversal of DOACs, without increasing the underlying risk of thrombosis. Andexanet alfa to reverse FXa inhibitors has been approved by the FDA recently. Evidence supporting non-specific reversal therapies including PCC, aPCC, or recombinant factor VIIa is still limited in terms of clinical outcome data. Administration of PCC or aPCC may be considered in addition to supportive measures for patients with severe or life-threatening bleeding.

Most importantly, the best way to treat a bleed related to a DOAC is to prevent it by using the right drug at the right dose in the right patient and by withdrawing anticoagulation in patients without an indication for such therapy.

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